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EXAMINER	
DRABIK, C	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/508,516	Applicant(s) BEBBINGTON ET AL.	
	Examiner Christopher Drabik	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sh et with th corr spondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26, and 28-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26 and 28-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Detailed Action

Applicant's election of claims 1-28, 30 and 42 in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)) and the requirement is made **FINAL.**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 appears to be an incomplete claim. The product claimed in the first phrase as "A retroviral vector comprising a functional splice donor site and a functional splice acceptor site;" is inappropriately associated with the phrases beginning with: "wherein the retroviral vector is derived from a retroviral provector;" and continuing to the end of the claim. It is unclear whether the retroviral provector described in the claim is or is not capable of producing a retroviral vector as described in the first phrase, because it is uncertain whether the retroviral vector has functional splice donor and acceptor sites or is merely providing sequences which might be modified to produce (i.e. capable) functional splice donor and acceptor pairs. This point is raised not on the basis of whether the splice donor/acceptor pair is in appropriate

orientation such that they might be functional, but rather whether the sequences themselves are functional. Claims 2-26, 28, 30 and 42 are also rejected based on there depending from Claim 1.

Claims 4, 7, 8, 11 and 12 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of these claims directly confer the idea that the retroviral vector proceeds from a provector as described in Claim 1. Since it has been established that the retroviral vector as defined is not consistent with the construction of the provector, Claims 4,7,8,11 and 12 are properly rejected under 25 USC 112 second paragraph as being indefinite.

Claim1-3,5,9,12,13,19,21,22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 21, and 22 recite the word "derived". The term "derived" renders the claims indefinite because the term merely indicates a source. The final product may have gone through any number of derivations such that it is not clear as to what applicants intend to claim.

Claims 1-3, 13 and 19 recite the term capable. The use of "capable" renders the metes and bounds of the claim indefinite. The term capable anticipates an infinite set of possibilities which ***might satisfy a claim***. For example, in Claim 1 applicant claims

sequences ***capable*** of functioning as splice donor and acceptor sites. Any sequence of DNA might be ***capable*** of functioning as a splice donor or acceptor site.

Claims 9, 11, 24 and 25 recite the term "obtainable". This is an open term which also does not adequately define the thing claimed. The term does not clearly define he source of the material because it implies that the claim includes sources other than that recited in the claim or disclosed in the specification.

Claim 12 recites the term "preventable." This term is unclear in that does not adequately point out the claimed effect. It is not specified whether splicing is or is not prevented. There is an infinite set of sequences which will not facilitate splicing.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 appears to be claiming two materially different inventions. In Claim 25 both a cell and a retroviral particle is claimed. Since the retroviral particle is not related to the cell, it is not clear what the applicant means to claim. It is suggested that applicant amend Claim 25 such that the invention claimed is clearly pointed out.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 26 applicant claims a retroviral vector or a viral particle or a cell or a retroviral particle. Since each of these inventions are materially

distinct and unrelated to each other it is unclear what the applicants deems as the invention claimed. It is suggested that applicant amend Claim 25 such that the invention claimed is clearly pointed out.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 28 begins "A method comprising.....", but later reads "... or a viral particle..." It appears that Claim 28 is inappropriately drawn to both a method and a product. Claims cannot be drawn to both a method and a product within the same claim. It is suggested that applicant amend Claim 28 such that the invention claimed is clearly pointed out.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26,28, 30 and 42 rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for the selective expression of the hygromycin - neomycin gene pair or the hygromycin-p450 gene pair does not reasonably provide enablement for all potential NOIs. While it is not questioned that one of skill in the art could easily generate the retroviral constructs disclosed in the instant application, the specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The nature of the invention claimed in Claims 1-26,28, 30 and 42 is a vector which upon transduction yields an activated splice donor/acceptor. The translocation of the splice donor site to the 5' of the splice acceptor site is achieved by reverse transcription of a parent vector. Insertion into the host cell's genome of the reverse transcribed DNA originating from the parent vector results in a provirus which has a functional intron. This intron may contain an NOI which can be a gene of interest. Because the gene of interest is within the intron no protein from the gene will be expressed due to splicing out of the sequence in mRNAs transcribed from the provirus. Further, expression of a second gene of interest (second NOI) downstream of the splice acceptor site is activated because of the functioning intron.

The construction of retroviral vectors for the selective expression of foreign genes is incompletely predictable. In describing the general nature of designing retroviral vectors Jolly remarks "It is worth noting that building retroviral vectors is still a mixture of art and science. Many creative ideas require multiple design attempts before performing anywhere close to desired." (Jolly D Viral Vector Systems for Gene Therapy (1994) Cancer Gene Therapy 1(1) see page 53) Although the applicants of the instant application have suggested a number of genes which might be used in there vector, they have supplied working examples for two pairs of NOI's (hygromycin/ neomycin and hygromycin/cytochrome p450). Particularly relevant to the design of the vectors described herein is the potential of cryptic splice donor/acceptor sites arising in NOIs

and the amount of experimentation required to design vectors which are free of such sites

The presence of cryptic splice sites becoming activated in retroviral transcripts in transduced cells has been well established. For example, McIvor et al describe the activation of a cryptic splice donor site in the retroviral backbone of a vector construct engineered to contain the human purine phosphorylase gene. (McIvor RS, Deletion in a recombinant retroviral vector resulting from a cryptic splice donor signal in the MoMLV envelope gene. (1990) Virology 176:652-55, see page 653 first paragraph). Zaboikin and Scheuning report poor expression of the MDR1 gene in retrovirally transduced HeLa cells resulting from unexpected splicing events. (Zaboikin MM and Scheuning FG Poor expression of MDR1 transgene in HeLa cells by bicistronic MoMLV-based vector (1998) Human Gene Therapy, 9:2263-2275, see Abstract)The splicing events occurred within the gene transcript itself and was more likely to occur in HeLa cells than in cells of canine origin (CTAC cells). This result confirmed previous observations of Sorrentino et al regarding the transduction of mice with retroviral constructs containing the MDR1 gene. (Sorrentino et al (1995) Blood 15;86(2):491-501).

Indeed, several members of the inventive entity have reported that one of the constructs specified in the instant application reveals a cryptic splice site in the CAT gene. In their paper, Ismail et al show that placement of the SV40 promoter upstream of the CAT gene in a pICUT vector resulted in no CAT expression from transduced cells. (Ismail SI et al, Split-intron retroviral vectors:enhanced expression with improved safety features (2000) Journal of Virology 74(5):2365-2371 see page 2369) It is important to

note that the pICUT vector is set forth as an example in the instant application. They reasoned that the lack of CAT expression was most likely due a splicing reaction between sequences in the SV40 promoter and the CAT gene. Removal of the SV40-neo cassette resulted in the functioning of the CAT gene.

Crucial to the functioning of the invention claimed in Claim 19 is that incorrect splicing events within the retroviral construct do not occur. For example, unpredicted splicing events within an NOI or between the first and second NOI can result in nonfunctional or partially functional constructs. In essence, any given NOI or pair of NOI's must be tested to determine whether they are capable of functioning as claimed. Further, specific sequences of the vector backbone may contribute to unwanted splicing events. Undue experimentation is required to determine whether a given NOI can be inserted into the vector without introducing unwanted splice sites and the invention cannot be used as claimed.

In addition to the reasons set forth above, Claims 20, 25,26 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 26 of the instant application is drawn to the use of a retroviral vector or a retroviral particle for use in medicine. This claim encompasses the therapeutic treatment of human disease states as disclosed in the specification (see e.g. paragraph bridging pages 50-51). Claim 20 is drawn to a retroviral vector for in vivo use. Claims 25 and 28

are drawn to cells transfected or transduced with a retroviral vector or a retroviral particle produced as the result of a productive infection of said cells. While claims 25 and 28 do not recite gene therapy as an intended use for said retroviral vector or retroviral particle, claims recite the transfection or transduction of cells as the intended usage. This method of treating cells encompasses in vivo uses. When reading the claims in light of the specification, a reasonable interpretation of in vivo usage of said retroviral vector or retroviral vector includes there use in gene therapy. Indeed, applicant discloses on the first page of the instant application: "...the present invention relates to inter alia a novel retroviral vector useful in gene therapy" (lines 13 and 14).

As claims encompassing gene therapy these inventions are anticipatory of a treatment which alleviates a disease state. Gene therapy as a means for curing or alleviating human disease states remains incompletely proven and unpredictable. Verma et al. In reviewing the art of gene therapy writes: "Although more than two hundred clinical trials are currently underway... there is still no single outcome that we can point to as a success story" (see Verma et al., page 239, col. 1). More recently, Patterson, directing remarks to the Senate subcommittee on Public Health stated :"To date more than 4000 patients have participated in gene therapy studies (in 372 NIH registered trials)... Only one percent of the trials (3 protocols) have progressed to phase III efficacy studies. Thus, most human gene therapy clinical trials have been focused on safety rather than efficacy. For this reason, it is perhaps more appropriate to refer to this technology as gene "transfer" rather than 'gene therapy', until there is more evidence for

the therapeutic benefit of this technology." (Patterson A (2000) http://www4.od.nih.gov/oba/patterson2-00.pdf see page 2, 2nd full paragraph).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. [See Eck et al Gene-Based Therapy in *The Pharmaceutical Basis of Therapeutics*, *9th ed* (1996) McGraw Hill ¶ bridging pages 81-82.]

The instant application, while providing a number of examples for the construction of gene transfer vectors, does not provide a working example of a ***therapeutic*** retroviral vector. The examples illustrate the construction of several marker gene vectors (β-galactosidase, hygromycin, neomycin) and vectors containing the cytochrome p450 gene, but give no examples showing the effectiveness of the vectors in vivo in treating any human disease state.

It is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples

provided, and the breadth of the claims that it would require undue experimentation to practice the invention(s) of claims 25,26 and28

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 9,10, 12-14, 18-25 are rejected under 35 USC 102(b) as being clearly anticipated by Morgenstern et al. (Morgenstern, JP and Land, H (1990) Advanced mammalian gene transfer:high titre retroviral vectors with multiple drug selection markers and a complementary helper-free packaging cell line. Nucleic Acids Research 18(12):3587-96)

Since it has been established that claim 1 is incomplete, for 35 USC 102(b) examination purposes the claimed invention is taken to be a retroviral vector containing functional splice donor and acceptor sites comprising one or more nucleotide sequences of interest (NOI). In so far as the invention(s) pertain to a retroviral vector with functional splice donor and acceptor sites flanking one NOI and potentially comprising other NOIs , there is a large body of prior art which reads on the claimed invention. It should, however, be noted the 102(b) rejections given below could be overcome if the claim language is sufficiently modified to clarify the source of the retroviral vector, the nature of the provector and the relationship of the provector to the retroviral vector.

Morgenstern et al describes a retroviral vector termed prZNSV(X) comprising a functional splice donor and acceptor site. Further, the disclosure of Morgenstern et al provides a description of a vector which contains two sequence which can be construed as NOIs as described by the instant application. The configuration of the splice donor/acceptor sequence and the NOIs is such that claims 1-4 are clearly anticipated. It should be noted that in Claim 2, the phrase ;"wherein the third NS is capable of yielding a non-functional splice site" adds little information to the claim. Any sequence of DNA could be capable of not facilitating splicing.

The plasmid prZNSV(x) includes coding sequence which confers resistance to neomycin. This aspect of Morgenstern's disclosure clearly anticipates Claims 5 and 6 of the instant application. Claim 5 and 6 is anticipated in that antibiotic resistance can be considered both a diagnostic agent and also confer selectability. Resistance to neomycin can be considered as diagnostic of a successful transfection/transduction.

Claim 9 of the instant application is drawn to a retroviral vector as outlined in claim 1 also containing a nucleotide sequence "obtainable" from a virus. Claim 10 limits the claims of Claim 9 in that the nucleotide sequence is specified as an intron or part thereof. The sequence comprising the splice donor site in prZNSV(X) anticipates the limitations of both claims 9 and 10: The sequence 3' of the splice donor site in prZNSV(X) is part of an intronic sequence and also of viral origin, hence Claims 9 and 10 are clearly anticipated.

Claim 12 of the instant application is drawn to a retroviral vector as outlined in claim 1 also containing a packaging signal. The term "preventable" in this claim is read

to include sequences that can and cannot facilitate splicing . Since the vector described by Morgenstern produces virus which are packaged into infectious particles (see figure 2 legend page 3589)it is inferred that the sequence contains a packaging signal are present. (Cepko et al in the original paper describing pZipNeoSV(X), the parent vector of prZNSV(X), state that sequences necessary for encapsidation are present – see page 1053 col 2, 2nd full paragraph).

Claim 13 is drawn to the retroviral vector of claim 1 wherein the second NS is placed downstream of the first NOI. The term "capable" in this claim does not specifiy a particular attribute of the vector. The vector prZNSV(X) contains a splice acceptor site which can be considered a second NS. The hygro gene can be considered a first NOI and therefore the configuration of the retroviral vector of Claim 13 is clearly anticipated.

Claims 18 and 19 are drawn to a retroviral vector as described in claim 1 which also comprises a functional intron. Claim 20 specifies that the target site of the vector as a cell. The specification in Claim 19 that the vector "...is capable of restricting expression..." does not clearly define whether the vector claimed does or does not have the ability to restrict expression. Since the hygromycin coding sequence in prZNSV(X) can be spliced out, the vector contains a functional intron and, hence, clearly anticipates the retroviral vectors claimed in Claims 18 and 19. Morgenstern et al uses prZNSV(X) to infect tissue culture cells, clearly anticipating the limitations of Claim 20.

Claims 21 and 22 are drawn to a retroviral vector as described in claim 1 further specifying the source of the vector or pro-vector sequences. Claim 21 specifies that the source is a murine oncoretrovirus or a lentivirus. Claim 22 specifies that the source of

viral vector sequence is MMLV, MSV MMTV, HIV-1 or EIAV. It is important to note the applicants recite that the retroviral vector or provector is "derivable " from a specified source. This does not require that the ultimate structure of the retroviral vector have any discernable characteristic of the source virus. The source of prZNSV(X) is the murine oncoretrovirus Moloney murine leukemia virus (MMLV) and, therefore, claims 21 and 22 are clearly anticipated by Morgenstern et al.

Claim 23 is drawn to an integrated provirus having the characteristics of the retroviral vector of claim1. Morgenstern et al make reference that retroviruses in there disclosure are isolated from stable producer cell lines (see paragraph bridging pages 3588-89). Since it is unlikely that the primary retroviral vectors exist as stable episomes, it is inferred that the secondary retroviruses arise from stable integration events and, therefore, the primary retroviral vectors are converted to proviruses.

Claim 24 is drawn to "A retroviral particle obtainable from a retroviral vector..." For examination purposes of this claim, It is taken to mean that "obtainable from" means the particle was produced from a productive infection using the retroviral vector of Claim 1. This claim, however, reads on other means of generating infective particles. It is unclear whether any intermediate step of introducing the virus to cells to produce the particle is meant or implied. For example, a retroviral particle as described in Claim 24 can be produced from the combination of the retroviral vector with lipids to form liposomes. In so far as the retroviral particle arises from a productive infection, the disclosure of Morgenstern et al clearly anticipates Claim 24 since retroviral particles were derived from prZNSV(X).

Claim 25 is clearly anticipated by Morgenstern since prZNSV(X)was used to infect tissue culture cells.

Claims 15-17 are rejected under 35 USC 102(b) as being clearly anticipated by Takeda et al. (Takeda S-I et al (1985) Construction of chimeric processed immunoglobulin genes containing mouse variable and human constant region sequences Nature 314: 452-454) Claims 15-17 are dependent upon claim 1 and therefore the invention (s) described in Claims 15-17 is a retroviral vector comprising an NOI flanked by functional splice donor and acceptor sites. In addition, the retroviral vector contains a nucleotide sequence which codes for 1.) an immunological molecule (Claim 15), or 2.) an immunoglobulin (Claim 16), or 3.) an immunoglobulin heavy chain variable region.

Takeda et al teaches a recombinant retroviral vector carrying genomic heavy cahin variable –diversity joining and constant region genes. (see page 453, figure 1 and figure 1 legend.) Several splice donor/acceptor pairs are present which flank sequences that can be nucleotide sequences of interest, hence the limitations of claim 1 are clearly anticipated. Since the vector also comprises an immunoglobulin heavy chain variable region, the specific claims of Claim 15-17 are clearly anticipated.

Claims 9-11 are rejected under 35 USC 102(b) as being clearly anticipated by Kriegler et al (Kriegler M et al (1984) Transformation mediated by the SV40 T antigens: seperation of the overlapping SV40 early genes with a retroviral vector Cell 38:483-

491). Claims 9-11 are dependent upon claim 1 and therefore the invention (s) described in Claims 9-11 is a retroviral vector comprising an NOI flanked by functional splice donor and acceptor sites. In addition, the retroviral vector contains a nucleotide sequence that is: 1.) obtainable from a virus (Claim 9), or 2.) an intron or part thereof (Claim 10), or 3.) an intron obtainable from the small-t intron of SV40 (Claim 11).

Kriegler et al describes retroviral vectors containing the coding sequence for the early genes of SV40. (see page 484, figure 1)Vectors pFVX and pEVX includes the overlapping genes of T and t antigen comprising a functional t intron. These attributes clearly anticipate the requirements of Claims 9-11. Since the sequence comprising the intron can also be an NOI, the requirements of Claim 1 are also clearly anticipated.

Conclusion

No claim examined in the restricted set of claims is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Drabik whose telephone number is 703-605-1156. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 703-305- 4051. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234. Questions regarding review of formality issues may be directed to Kim Davis, the patent analyst assisting in this application. She may be reached at 703-308-4242.

Deborah Clark

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